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Title: REQUEST FOR PROPOSALS REGARDING COMMERCIALIZATION OPPORTUNITY FOR ADVANCED TISSUE-ENGINEERED HUMAN ECTYPAL NETWORKS ANALYZER (ATHENA) TECHNOLOGY

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REQUEST FOR PROPOSALS REGARDING COMMERCIALIZATION OPPORTUNITY FOR ADVANCED TISSUE-ENGINEERED HUMAN ECTYPAL NETWORKS ANALYZER (ATHENA) TECHNOLOGY

Los Alamos National Security, LLC (LANS) is the manager and operator of Los Alamos National Laboratory (Los Alamos) for the U.S. Department of Energy National Nuclear Security Administration under contract DE-AC52-06NA25396. Los Alamos is a mission-centric Federally Funded Research and Development Center (FFRDC) focused on solving critical national security challenges through science and engineering for both government and private customers. **LANS is seeking an industry partner(s) for development and commercial deployment of its Advanced Tissue-engineered Human Ectypal Networks Analyzer (ATHENA) technology.**

ABSTRACT

LANS is seeking development and commercial deployment of its Advanced Tissue-engineered Human Ectypal Networks Analyzer (ATHENA) technology. ATHENA is a milli-scale surrogate human organ system, coupled with highly sensitive analytical technologies, developed for screening of lead compounds, testing of medical countermeasures, and toxicity testing by recapitulating the human metabolic response. ATHENA includes the pulmonary model PuLMo, which won an R&D 100 Award this year. Using ATHENA as a starting point, Los Alamos is seeking to engage one or more industry partners towards the development of a small *in vitro* predictive diagnostic platform supporting multiple human organ constructs in communication with each other that accurately recapitulates human metabolic response. The platform should be flexible, user-friendly, and reliable. It should also be optimized for use in the drug development pipeline by generating data to support *in vivo* testing and evaluation plans for investigational products, and should be geared towards acceptance by regulatory agencies such as the FDA as an alternative to, or replacement of, *in vitro* and possibly *in vivo* techniques.

WHAT LANS IS SEEKING

Prior to clinical trials, drugs and new compounds must be characterized in pre-clinical studies. Current methods for pre-clinical data rely almost exclusively on *in vitro* and *in vivo* models. Conventional *in vitro* techniques lack the complexity of human organs, and the current gold standard of animal testing has proven to be an inadequate substitute. This fact is recognized by regulatory agencies such as the FDA, as well as a plethora of NGOs. However, despite impressive advances in 3D culture and engineered organs, there is still no viable alternative to these methods. The ATHENA fluidic bio-assessment platform has begun to address this need.

Over the past 3+ years, Los Alamos scientists have developed a milli-scale surrogate human organ system, coupled with highly sensitive analytical technologies. Dubbed the Advanced Tissue-engineered Human Ectypal Networks Analyzer (ATHENA), the platform is a human organ construct developed for screening of lead compounds, testing of medical countermeasures, and

toxicity testing by having the ability to look at primary and secondary metabolites and to recapitulate the human metabolic response. This enables determination of the fate of toxins entering the system under conditions that emulate critical *in vivo* conditions, unlike typical *in vitro* assays.

Estimated at around $75 billion in 2015, drug development R&D represents an enormous opportunity to improve countless lives. Using ATHENA as a starting point, Los Alamos is seeking to engage one or more industry partners towards the development of a small *in vitro* predictive diagnostic platform supporting multiple (2 or more) human organ constructs in communication with each other (e.g. via a universal media), that accurately recapitulates human response in order to predict human-relevant safety, efficacy, and pharmacokinetics of drugs. Ultimately, the platform should be optimized for use in the drug development pipeline by generating data to support *in vivo* testing and evaluation plans for investigational products.

Consideration should be given to how the platform may be used toward development of specialized therapeutics such as medical countermeasures against radiological, chemical or biological agents for which it is unethical to conduct human clinical trials. The platform should be flexible, user-friendly for benchtop use, able to integrated with existing RDT&E pipelines, and have the ability to operate in standalone mode for long periods of time. Finally, the platform should be geared towards acceptance by regulatory agencies such as the FDA as an alternative to, or replacement of, *in vitro* and possibly *in vivo* techniques.

ATHENA BACKGROUND & RECENT DEVELOPMENT

ATHENA currently consists of four organs (heart, lung, liver, and kidney), seeded with primary human cells and integrated onto a fluidic platform. LANS is developing a universal media to perfuse all four organs to enable their communication. To date, the liver, lung and heart organ modules are well-developed, and the liver and heart have been interconnected to function together via a universal media. By designing in the milli-scale, all organs and fluid amounts are of large enough volume to allow multiple samples to be taken for various clinical assays. The kidney is currently in early-stage R&D. We plan to integrate additional organs onto our proprietary fluidic platform to function together. The ATHENA team has investigated toxicology and efficacy endpoints of collagen production in a skin model, and of cell growth in a bone model. Future plans include development of several organs, including skin, cornea, retina, gut, nasal tissues, and immune tissues for similar and larger-scale projects. In addition, ATHENA has been conceived of as a platform to modeling and understanding the effects of radiotherapy and radiosurgery. ATHENA has been a multi-partner effort. In addition to coordinating this larger effort, Los Alamos scientists have focused on three specific areas of R&D: the fluidic platform for integration of all organ modules, universal media for perfusing all organ modules, and a lung organ module (nicknamed “PuLMo” for Pulmonary Model, a 2016 R&D 100 Award Winner).

The platform integrating all organ modules does so via a unified fluidic network that connects all organs to each other, as well as to reservoirs and other inputs and outputs that can be configured per specification. This shoebox-sized platform comprises various pumps, valves, reservoirs, and a multilayered microchannel network to facilitate long-term operations in an efficient, sanitary and simplified manner. In our ongoing R&D we are making significant advances towards making ATHENA, PuLMo, and other related technology useful for a wide range of applications in contemporary health and medicine. Fabrication methods and materials are selected on the basis of compatibility with large scale production, sterilization techniques, and long-term operations. We have engineered a ‘breathing assist’ that allows PulMo to mimic inspiration/expiration from ambient air in a manner very similar to the human lung. PuLMo is designed to recapitulate the flow profile of a lung by incorporating circular shaped alveolar structures and branched air-way network.

Using custom software developed for optimizing media, five different media have been formulated and tested on various organ configurations. The media formulations are designed to support growth, viability, and function of one or more than one cell type, tissue type, or organ. A number of these formulations are basal media, to which growth factors, sugars, and other components are added in a systematic manner to allow the growth and viability and function of several different human cell

types. To achieve optimal cell functionality and longevity, additional components are added to this basal media as well. We have successfully cultured liver cells (~1 week) and our liver bioreactor (approximately 1 week) and maintained beating heart cells (approximately 2 weeks) in one of the universal media for several days.

PuLMo, A PULMONARY MODEL (2016 R&D 100 AWARD WINNING TECHNOLOGY)

PuLMo is a miniaturized, *in vitro*, tissue engineered artificial lung that is designed to emulate important biophysical features of the human lung. It is made of a combination of plastics via a unique fabrication method, which is a combination of subtractive and additive manufacturing. We use commercial off-the-shelf (COTS) finished (e.g. sheets, films) or semi-finished (e.g. tapes) materials for fabrication. If a suitable COTS material is not available, we fabricate it using microfabrication and other in-house techniques. PuLMo represents an all-inclusive suite of technologies, including structural features such as branched airways, inflatable alveoli, and air-liquid interfaces. Importantly, PuLMo simulates breathing in a physiologically relevant manner by creating a vacuum inside the microfluidic chambers via novel membrane actuation that we call "microfluidic aspiration". Additionally, PuLMo is configurable in order to be able to select the set of physiological functions to recapitulate. Please see the R&D 100 Award information package (PuLMo RD 100_abridged_LAUR_1622344) PuLMo's 2016 R&D 100 Award webpage for further information.

LANS INTELLECTUAL PROPERTY

ATHENA technology is at the intersection of several intellectual property (IP) portfolios. Successful commercialization of the ATHENA platform may or may not leverage the listed patents and/or complementary portfolios.

- Bioassessment
    - Bio-Assessment Device and Method of Making the Device (LANS Ref. No. S 133,109.001, PCT App. No. PCT/US2015/052039)
    - Sample Platform and Methods of Use (LANS Ref. No. S 133,261.001; U.S. App. No. 62/212,254)
    - Devices For Fluid Management and Methods of Making and Using the Same (LANS Ref. No. S 133,286.001; PCT App. No. PCT/US2015/052043)
    - LANS also has the following portfolios which may be leveraged towards ATHENA commercialization: Affinity reagents, Biophysics, Complex systems modeling & simulation, Computational multiphysics, Computational & theoretical biology, Experimental models of disease, Genomics, High-throughput gene cloning, Novel bioassay development, Protein analysis.
- Bioengineered materials and biomaterials
    - Multi-Organ Media Compositions and Methods of Their Use (LANS Ref. No. S 133,295.001; PCT App. No. PCT/US2015/052046)
    - Patterned Neuromuscular Junctions and Methods of Use (LANS Ref. No. S 133,124.001; PCT App. No. PCT/US2015/062506)
    - LANS also has the following portfolios which may be leveraged towards ATHENA commercialization: Engineered membranes, Soft & composite nanomaterials.
- Hybrid manufacturing; Fabrication & assembly
    - Reversibly bonded microfluidic devices and method of making the device (LANS Ref. No. S 133,381.000; U.S. App. No. 62/401,663)
    - LANS also has the following portfolios which may be leveraged towards ATHENA commercialization: Additive manufacturing, Advanced materials.
- Platform automation & optimization; Analytics interface; and other engineering solutions

  - Magnetically Controlled Valves and Pumps (LANS Ref. No. S 133,380.000; U.S. App. No. 62/322,622)
  - Microfluidic aspirator and methods of making and using the same (LANS Ref. No. S 133,379.000; U.S. App. No. 62/322,577)
  - Devices for co-culture and methods of making and using the same (LANS Ref. No. S 133,382.000; U.S. App. No. 62/384,451)
  - LANS also has the following portfolios which may be leveraged towards ATHENA commercialization: Instrumentation, Reconfigurable hardware, Remote sensing, Sensors, Sparse signal recovery, Spectroscopy.
- Software development and user interface
  - Custom perfusion control software for fluid monitoring and management of ATHENA platform
  - LANS also has the following portfolios which may be leveraged towards ATHENA commercialization: Cybersecurity & cryptography, Deep learning, Informatics, Machine Learning, Reconfigurable software, Video analytics.

Please note that the U.S. Government retains a worldwide, royalty-free, non-exclusive right to practice any LANS-owned patents and/or copyrighted software. Accordingly, any entity will have open access to LANS patents and copyrights in performance of a Government contract.

COMMERCIALIZATION PROPOSAL

LANS is willing to explore various and/or multiple mechanisms to ensure the vitality of its internal research and development program for government customers while accelerating the broader adoption and deployment of this technology for commercial applications with private sector partners. Depending on respondent's Commercialization Proposal and on availability of LANS technical staff, there may be opportunities to partner with Los Alamos technical staff to execute on your Commercialization Proposal. Please visit Los Alamos' Feynman Center for Innovation website on partnering for additional information.

For all entities interested in submitting a Commercialization Proposal and also holding a current Nondisclosure Agreement (NDA) with LANS, an informational webinar will be hosted on DATE. Information obtained during this webinar may be used in writing the Commercialization Proposal. You may submit questions in writing to athena@lanl.gov prior to the Q&A webinar. LANS will select collaboration partner(s)/licensee(s) based on a review and analysis of all Commercialization Proposals submitted for consideration. LANS reserves the right to not select any partner(s)/licensee(s). Your Commercialization Proposal should address the following:

- Company description;
- Description of interest in ATHENA and any relevance to company goals and product offering(s);
- Identification of ideal points of market entry for ATHENA, or plan for determining such;
- Business strategy for deploying ATHENA, or plan for determining such;
- Experience developing and commercializing similar technology;
- Financial and human resources available for developing and commercializing this technology;
- Any expertise that may be needed from the ATHENA team;
- Any specific IP for which licenses would be requested (please see above);
- Scope of license rights needed (please visit Los Alamos' licensing website for licensing details);
- Any experience working with FFRDCs;
- Any experience working with US Government entities (e.g. Department of Defense);
- Any questions you have for follow-on discussions.

SUBMITTING A COMMERCIALIZATION PROPOSAL

This Commercialization Opportunity RFP is made without prejudice to any form of collaborative arrangement, alliance, or number of entities. Ability and willingness to ensure compliance with U.S. Export Control law is a requirement. Those companies interested in pursuing this opportunity should direct a Commercialization Proposal to the undersigned before 11:59 MST on January 31, 2017. All communication regarding this RFP should be directed to Miranda Intrator, Business Development Executive, Feynman Center for Innovation, Los Alamos National Laboratory, 505.665.8315, mhi@lanl.gov. Please include "ATHENA Commercialization Opportunity RFP" in the subject line. Please properly mark any information that is considered proprietary or business-sensitive. LANS will supply an NDA to any U.S. company or person requiring it. We look forward to reviewing your ideas on how together we can rapidly advance this technology towards the commercial marketplace and accelerate deployment to the benefit of the U.S. economy.

Action	Date
Commercialization Opportunity RFP posted to FedBizOpps	TBD
Proprietary Q&A webinar (must hold NDA with LANS to participate)	January 19, 2017
Call responses due	February 16, 2017
Call decision notification to responding entities	March 9, 2017

ATTACHMENTS

- S133109 PCT Application and Figures.pdf
- S133124 PCT Application and Figures.pdf
- S133286 PCT Application and Figures.pdf
- S133295 PCT Application and Figures.pdf
- 2015_MRS_LAUR_1528330.pdf
- Bioscience_Seminar_Nath_April 2016.pdf
- Developing an Artificial Alveoli.pdf
- PuLMo RD 100_abridged_LAUR_1622344.pdf

AVAILABLE UNDER NDA

- S133261 Application and Figures.pdf
- S133379 Application and Figures.pdf
- S133380 Application and Figures.pdf
- S133381 Application and Figures.pdf
- S133382 Application and Figures.pdf